CMA committee report on Connaught Laboratories Ltd.

Dans son rapport sur les Laboratoires Connaught Ltée, le comité nommé par l'Association médicale canadienne donne une perspective historique et une description de la position présente de cette institution vis-à-vis de la Corporation de Développement du Canada et de Connlab Holdings Ltée. Il discute aussi plusieurs des critiques qu'on leur a adressées et qui peuvent intéresser les médecins.

Le Comité a conclu qu'il est essentiel pour le Canada d'être indépendant en ce qui concerne la fabrication de produits biologiques vitaux et que les Laboratoires Connaught Ltée pourraient remplir cette fonction à condition d'avoir:

- **L'assurance que le CDC et le gouvernement fédéral leur procureront les soutiens nécessaires;**
- **Un nouveau président, nommé dès que possible, qui soit capable de comprendre les problèmes spécifiques à cette industrie;**
- **Le soutien nécessaire à la recherche;**
- **La possibilité de recruter du personnel nouveau;**
- **De nouvelles installations et quelques améliorations aux installations existantes;**
- **Une organisation interne améliorée et des communications plus efficaces.**

Highlights of a report made by the Canadian Medical Association appointed committee on Connaught Laboratories Ltd. include a historical perspective and a description of the institution's present corporate setting. A sample of criticisms of interest to practising physicians is presented.

The committee concludes that it is essential for Canada to be self-sufficient in the manufacture of necessary biologicals and that Connaught Laboratories Ltd. could serve such a function provided there is, inter alia:

- **A clear commitment by the Canada Development Corporation and the federal government to provide necessary support;**
- **A new president quickly appointed, capable of understanding the nature of the industry;**
- **Adequate support for research;**
- **Recruitment of new staff;**
- **Renewal and renovation of facilities where necessary; and**
- **Improved internal organization and communication.**

Early in 1976 the Canadian Medical Association together with Connaught Laboratories Ltd. (hereafter to be referred to as Connaught) agreed to the striking of a CMA committee to study numerous criticisms of Connaught policies and products which had received wide publicity, particularly in the *Globe and Mail* in February 1975. These criticisms, as well as allegations, had caused many Canadian physicians to query Connaught products and their concerns had been expressed to the CMA on a number of occasions.

The CMA committee was directed, under its terms of reference, "to make a comprehensive report to the CMA and to Connaught Laboratories Ltd. (CLL), on the criticisms and allegations which have been made of CLL products, and to examine any aspect of CLL's operations which may relate to these criticisms and allegations."

It is easy to understand why Connaught's reputation was long inviolable if one examines its past performance. Such an examination reveals fundamental services which Connaught, throughout its existence, has offered Canada.

1. Provision of essential products for the treatment and prevention of disease

As far back as 1915 the laboratory from which Connaught evolved was manufacturing rabies and diphtheria antitoxins. The diphtheria antitoxin was distributed free by the Government of Ontario in the province and was sold elsewhere in Canada.

Over the ensuing decades, Connaught has provided virtually all Canada's insulin requirements, developed toxoids and vaccines, processed human blood products and, for a period of time, manufactured penicillin. Connaught's contribution to preventive medicine has been enormous.

2. Response to emergency needs.

Connaught's capacity in this respect is well illustrated by its role in two World Wars. It provided tetanus antitoxin to the wounded in World War I. When World War II began, Connaught was able to supply all Canada's armed forces with smallpox vaccine, tetanus toxoid, typhus vaccine, gas gangrene antitoxin, TAB and dried blood serum. By the end of the war it was manufacturing penicillin. (Nearly all the penicillin now used in Canada is manufactured abroad.)

3. International cooperation.

Connaught has made a major contribution to the World Health Organization's (WHO) smallpox eradication program. Not only did Connaught provide all the smallpox vaccine required by South America, it also conducted training programs, established smallpox vaccine production in other countries and supplied WHO with millions of doses of vaccine.

This summary was prepared by the committee and approved for *CMAJ* publication by Dr. R.C. Dickson, chairman. Reprints of this summary and copies of the full report are available from the department of communications, Canadian Medical Association, PO Box 8650, Ottawa K1G 0G8. Committee members were: Dr. R.C. Dickson (chairman), Halifax; Dr. C.J. Baines (secretary), Toronto; Dr. J.A. Dudgeon, London, England; Dr. F.T. Perkins, Geneva, Switzerland; Dr. J.C. Wilt, Winnipeg. CMA coordinator for the committee was Dr. J.S. Bennett, Ottawa.

4. Research.

In the mid 1940s a research proposal to develop a culture medium suitable for in vitro growth of human and animal cells was accepted although no practical consequence was foreseen at the time. The result was Formula 199, a culture medium which made possible the mass production of poliomyelitis vaccine in the early 1950s. Connaught has always been very active in insulin research, one achievement being the development of sulfonated insulin.

5.

Finally, Connaught's history reveals that close cooperation with government has always worked to the benefit of both, and of the nation. This has been true since 1915 when Connaught began producing tetanus antitoxin needed by the wounded in World War I. The antitoxin was produced with capital assistance from the Ministry of Defence. Then, as now, cooperation was essential. It bodes ill for Connaught that recently various Canadian health ministries have, for different reasons, turned to foreign suppliers for necessary biological products.

In spite of its many achievements, Connaught now faces an uncertain future and the reasons for this are multiple. Before exploring them however, it is necessary to understand that corporate structure in which Connaught is presently situated and then to discuss the criticisms and allegations of most importance to physicians.

By 1970, the University of Toronto, which still owned Connaught, realized that large capital investment was needed to improve Connaught facilities; construction of new buildings and renovation of existing buildings were required. Since

the Government of Ontario could not be persuaded to give the necessary funds, the university decided to sell Connaught.

In June 1972, Connaught was purchased by the Canada Development Corporation (CDC). CDC's purposes are clearly stated in its 1975 annual report:

i) To develop and maintain strong Canadian controlled and managed corporations in the private sector.

ii) To widen the investment opportunities open to Canadians.

iii) To operate profitably and in the best interests of all the shareholders.

Table I reveals Connaught Laboratories Ltd. to be one of many purchases made by CDC through Connlab Holdings Ltd.

Of major importance in understanding the precariousness of Connaught's present state is an awareness of the dichotomy of purpose which occurs when profits are sought from a purely "biologicals" facility such as Connaught. The implication of this dichotomy will be discussed later.

Criticisms and allegations

The list of specific criticisms and allegations which have been made is very long. Many criticisms are unfounded. Two, which probably have received the most public attention, relate to smallpox vaccine and insulin, and in these two instances the committee found Connaught to be quite blameless. Criticisms follow, selected because they are believed to be of interest to practising physicians.

1. Smallpox vaccine

a) The Bangladesh incident was described luridly in the press: it was said that the Canadian vaccine was causing disease. It was not causing disease. No WHO official ever claimed it was causing disease. The report was in error.

Of approximately 48 million doses of smallpox vaccine supplied to WHO by Connaught, 8000 vials were found to be unsatisfactory. Among those vaccinated with this vaccine there was a much greater than usual number of non-takes. Investigation revealed that the butyl stoppers of the vials had retained moisture and that, under conditions of high temperature and humidity which prevailed in Bangladesh, the moisture caused the vaccine to deteriorate. When the vials were stored at temperatures of 10°C or less, the deterioration did not occur. This explained why neither Connaught nor any other manufacturer had previously detected the problem.

Connaught discovered that submitting the vials to a drying phase after autoclaving removed the moisture from the butyl stopper and prevented deterioration of the vaccine. This discovery was useful for all manufacturers. It is important to note that at no time did WHO rebuke Connaught for this incident and that WHO continued to use Connaught smallpox vaccine. Connaught-produced vaccine has played a major role in the successful smallpox eradication program carried out by WHO.

b) In Canada it was charged that Connaught's smallpox vaccine was causing an increased number of adverse reactions due to increased potency. BOB (Canada) found that the potency was unchanged. Adverse reactions followed unnecessarily energetic application of the vaccine. Other adverse reactions occurred in people for whom vaccination was clearly contraindicated.

2. Insulin

A vial of Insulin Toronto was found in a carton labelled NPH Insulin in the home of a patient. After this incident was reported, a search of Connaught stocks failed to reveal any further packaging errors. The committee noted that tampering with packages, after they have left Connaught, is possible (since refrigerators storing insulin in pharmacies may be accessible to the public) and is beyond Connaught's control. Connaught has instituted a new system of packaging incorporating colour and bar coding to diminish the likelihood of a recurrence of this problem.

3. Human blood products

a) Connaught was criticized for not subjecting exported serum albumin to Canadian standards. However, it is impossible to impose final standards on an intermediate bulk product, such as human albumin, which will undergo further processing in the country of destination. Connaught devised a method, licensed by BOB (Ottawa) of rendering plasma nonpyrogenic. The final processor is responsible for the potency, safety and purity of the final dosage form.

b) Connaught was said to have reacted in a casual manner to adverse reactions following the use of immune serum globulin. To the contrary, Connaught sought information from other Canadian centres following the initial report of adverse reactions occurring in a group of Halifax nurses. Distribution of the involved lot was halted and unused material recalled from the market. All lots on retest met all criteria for potency safety and purity. More elaborate tests revealed some impurities isolated by electrophoresis, an increase in histamine-like activity and higher than normal titers of blood groups A and B.

c) The committee agreed with the allegation that there had been a delay in getting Factor VIII into production.

d) On the basis of the committee's own site inspection of the blood fractionation plant and after examination of a peer review committee report dated April 1976, the committee believes that there is a need for:

- Improvement in the separation of plasma and its transportation from the Red Cross to Connaught;
- Improvement of working conditions in the plant;
- Modification of fractionation procedures to increase the quality and quantity of products;
- Modernization of some equipment;
- Increased efficiency of final filling procedures;
- A cost accounting evaluation of various stages of the operation, and
- Improved liaison between the Red Cross and Connaught.

4. Multiple antigen vaccines

a) It was charged that three lots of DT-polio vaccine were released in spite of controversy about the diphtheria toxoid component and without the bureau of biologics (BOB) Canada being notified. The committee agrees that there was controversy and that BOB (Canada) was not notified prior to release.

The diphtheria toxoid component "failed" the Greenberg test, a test for identity which was not used outside Connaught and is used there no longer. However, the failure occurred only in a single group of guinea pigs which may have had coccidiosis when challenged. A different strain of healthy guinea pigs, when vaccinated with the same product, did survive challenge with diphtheria toxin.

The first lot of DT-polio in question was released Oct. 16, 1973 because it was of satisfactory potency, because it was to be used for recall doses only and because it was urgently needed. It was released by the director of quality control on Oct. 12 conditional to the unanimous agreement of his senior scientific colleagues; this agreement was signed on Oct. 16. The second lot was released Feb. 15, 1974 by the scientific director. The third lot was released in the normal manner on Mar. 22, 1974, by the director of quality control.

The apparent overruling of the director of quality control in the case of the second lot occurred before evidence of the vaccine's efficacy was available. Subsequently the vaccine was shown to be satisfactory. In none of these three instances was BOB (Canada) informed prior to release as regulations require.

The committee believes that the director of quality control should have ultimate authority for the release of a product.

b) It was claimed that the incidence of whooping cough is increasing in Ontario as a result of three lots of DPT-polio vaccine being released with less than desirable pertussis potency. Confusion arose because USA requirements are 14 international units (IU) for pertussis potency in DPT-polio vaccine, based on the assumption that poliomyelitis vaccine has a deleterious effect on pertussis vaccine when the two are combined. Connaught's purified polio vaccine does not have this effect on pertussis potency and, therefore, USA requirements are not relevant for the Canadian product. Connaught's vaccine with a pertussis potency of 12.7 IU per total immunizing dose was sufficient. Furthermore, potency tests for pertussis are difficult to perform, have wide fiducial limits and do not permit one to differentiate a product containing 12.7 IU from one containing 14 IU.

Epidemiologic data for pertussis morbidity in Ontario demonstrate an increased incidence between 1972 and 1975, but this cannot be directly attributed to inadequate potency of Connaught vaccine. No decrease in potency has been demonstrated and many factors influence the reported incidence of pertussis.

c) Connaught was criticized for stubbornly persisting with unadsorbed vaccine and for not having done clinical trials on adsorbed vaccines which were exported. The committee was told that many Canadian physicians are reluctant to change from the unadsorbed vaccines with which they are familiar to the adsorbed vaccines. Where a biological is produced for export only, the requirements under the Food and Drug Act are quite different from those applicable when the product is for sale and use in Canada. BOB (Canada) does not impose its standards on products leaving the country; the purchasing country exercises its own quality control. Connaught should not be criticized for exporting a vaccine on which it has done no clinical trials.

The committee believes that use of adsorbed vaccines in Canada should be reconsidered by Connaught and the National Advisory Committee on Immunizing Agents.

5. Sabin vaccine (oral, attenuated, live poliomyelitis vaccine)

It was alleged that Connaught's Sabin vaccine did not meet USA and UK regulatory standards. In the past, when Sabin vaccine production and control facilities were inadequate, the vaccine itself continued to pass quality control tests. Although UK inspectors made adverse comments about the facilities, they continued to buy Sabin vaccine from Connaught. The committee was informed that Connaught chose not to sell Sabin vaccine in the USA because of fear of litigation associated with the use of live vaccines.

Major renovations were accomplished in 1975 to the two buildings used for Sabin production and control. The committee found these facilities to be acceptable.

6. Salk vaccine (killed poliomyelitis vaccine)

a) The composition of Salk vaccine was changed following an Ontario survey of 1100 subjects which indicated that the Type III virus component should be increased. Connaught was accused of changing the virus ratio (Type I: Type II: Type III) from 8:2:2 to 8:1:3 without notification of the Health and Welfare, health protection branch (HPB) in Ottawa. However documents shown to the committee reveal that the lot with the revised ratio was released by BOB (Canada) after Connaught had submitted its protocol for the vaccine. Therefore it must be concluded that BOB (Canada) was aware of the changed ratio before release of the vaccine.

b) Connaught was criticized because it released Salk vaccine while it was being reviewed in the USA for a questionable neurovirulence safety test. By releasing the lot Connaught was not violating Canadian regulations because BOB (Canada) had approved the release. Nine months later BOB (USA) also released the vaccine.

c) Connaught was charged with failing to carry out clinical trials for Salk vaccine developed on a multisurface cell propagator (MSCP) at a time when only trial lots had been made for in vitro and in vivo tests and when no clinical use was intended. It was recognized that an amendment to the existing Salk vaccine licence was required. Clinical trials have since been done with the MSCP Salk vaccine, the necessary data submitted to BOB (Canada) and application made for licence.

7. Measles vaccine

a) The committee was satisfied that there was no overlapping of personnel and services in the production of measles and Marek's vaccines, nor were measles and rubella vaccines ever produced in the blood fractionation unit. This was totally unfeasible and never contemplated.

b) Connaught was accused of not "pushing ahead" with the development of a measles vaccine using human diploid cell (WI 38) cultures. However, adaptation to such cultures would require extensive and expensive clinical trials and production has been postponed, a decision with which the committee concurred.

The committee found there had been unfortunate delays in applying for a licence for measles vaccine prepared in chick embryo fibroblasts.

Table I — Canada Development Corporation, Connlab Holdings Ltd.

Analco Inc.
Canada Pharmacal Co. Limited
Canada Pharmacal Co. (1975) Limited
The Canada Serum Company Limited
Comex Nederland B.V.
Connaught Biologics Limited
Connaught Laboratories Limited
Connlab do Brasil Industria e Comercio Limitada
OY Dumex AB, Helsinki
Dumex Australia (Pty.) Ltd., Melbourne
Dumex B. V. Haag
A/S Dumex (Dumex Ltd.), Copenhagen
Dumex GmbH, Hamburg
Dumex Lakemedel AB, Halsingborg
Dumex Ltd., Accra
A/S Dumex, Norway
Dumex (Pty.) Ltd., Johannesburg
Dumex SPA, Genoa
Nordic Pharmaceutical Company Ltd.
Nordic Pharmaceuticals Limited
Octo Laboratory Limited
Omnimedic Inc.
R. & L. Molecular Research Ltd.
Raylo Chemicals Limited
Spabec Ltée

c) Clinical trials performed with the new chick embryo fibroblast measles vaccine were said to be inadequate. The committee learned that the trials were done according to HPB requirements. Data from the trials have been submitted to BOB (Canada) where the decision whether or not to license the measles vaccine will be made.

Connaught: present and future

What are the underlying reasons for Connaught's uncertain future? A major factor is ambiguity of purpose. At the present time Connaught fulfills neither of the two conflicting functions demanded of it: it is unable to provide Canada with all necessary biologicals; it is not making a profit for the CDC shareholders.

The former is demonstrated by Canada's dependence on foreign sources for bulk vaccine for the swine influenza vaccination program with all its attendant problems. As for the latter, the committee knows of no institution which profitably engages in the manufacture of a wide range of biologicals alone. Institutions supplying biologicals operate in one of two ways. If they produce a wide range of necessary biologicals they are either subsidized by government or subsidized by profit generated from other products, such as pharmaceuticals. If the institutions choose to produce only biologicals which can generate profits and avoid necessary but unprofitable biological products, they can be self supporting.

A consequence of the second option is that the nation becomes dependent on foreign sources for necessary biologicals. With full awareness of this implication, a specific choice must be made. Is Connaught to be an institution producing a broad range of necessary biologicals, excellent in standard for national and international use? Or, will Connaught produce only those items which meet a criterion of profitability?

The committee acknowledges that expansion into the pharmaceutical field by Connlab Holdings Ltd. does provide an opportunity for profit-making. In addition, the export of some biologicals can undoubtedly be commercially profitable. However, it cannot be ignored that there are necessary biologicals which cannot generate profits.

A second factor compromising Connaught's future appears to be a reluctance to renew Connaught's physical plant. Although investment in new construction and renovation at Connaught has exceeded $4 million in the last few years, the committee was informed that a further investment of close to $40 million is needed. This sum, while large, is dwarfed by the importance of self-sufficiency for Canada in the biologicals industry. Essential national objectives are not always profitable. An intention to render Connaught profit-making on behalf of its shareholders diminishes the likelihood that the investment essential for its renewal and support will be made and unfor-

tunately also diminishes its prestige in the eyes of many physicians.

Thirdly, the declining commitment to research at Connaught cannot be ignored. Evident for more than a decade, this trend seems to have accelerated in the past 4 years. The staff themselves perceive this trend with distress. Documents shown to the committee indicate an increased emphasis on production rather than research; this emphasis is on short-term research related to production rather than on long-term research related to new products. The committee is convinced that a strong research program is essential to the continued existence of Connaught.

Only if there is a major commitment to research will Connaught be able to attract and retain well qualified scientific staff. Research will improve existing products and help develop new ones. The example of Formula 199 should not be forgotten. The public recognizes the need for medical research and is prepared to support it. Government should heed the public example. Government professes commitment to preventive medicine. It is important to realise that biologicals play a major role in preventive medicine and that research has been the foundation of product development. Reliance on provision of biologicals from outside Canada, particularly in the case of epidemics or pandemics, may well prove to be unwarranted and have catastrophic results for the Canadian public. The federal government must be persuaded that a biologicals industry is a national need and not a luxury.

Fourthly, the committee found that staff morale has been undermined. The continuing adverse publicity, inadequate direction, reduction in staff and uncertainty itself have all contributed to this end. There has been poor communication between the scientific staff and management, and even among the scientific staff a sense of isolation has developed. Major decisions have been made without consultation of senior scientific staff and decision making procedures are poorly understood. Uncertainty must be further enhanced by the present situation in which the appointment of yet another president is awaited.

All the problems discussed in these four broad areas are correctible, provided Connaught is given adequate leadership and necessary support. Without these, its future is grim.

Committee recommendations

In making these recommendations, the committee wishes to stress that its investigation revealed many of the allegations made against Connaught to be unfounded. The committee finds that the fundamental functions of Connaught have been conducted with a high degree of scientific integrity and it has full confidence in the quality of Connaught products.

A. *National*

1. Canada needs and should support a biologicals industry for both national needs and the export market.

2. Facilities producing biologicals should be financially supported by government subsidies.

3. Such financial support should underwrite completely the cost of:

- Production of biologicals which are essential for the health needs of the nation but which may be financially unprofitable;
- Stock-piling of necessary reserves of biologicals to cope with national emergencies;
- Provision of biologicals to developing countries as may be deemed necessary;
- Research.

B. *Connaught Laboratories Ltd.*

4. Connaught should be a facility producing biologicals for national needs and the export market. In addition to subsidies for the functions outlined in 3 above, Connaught must receive adequate funds so that its plant may meet modern standards. Renovation of some buildings and the construction of new ones are required.

5. Research must gain much higher priority and this without delay in order that Connaught regain its position in the forefront of the development of biologicals.

6. The new president of Connaught should be a scientist of high standing, preferably with an appreciation of the problems associated with the manufacturer of biologicals.

7. The scientific direction at Connaught requires complete reorganization with greater involvement of the senior staff in decision and policy making. It is undesirable for the scientific director tor to be chairman of the board.

8. An active cross-fertilization of ideas between universities and Connaught should be encouraged. This could be achieved in a number of ways, such as

- The establishment of a peer review committee involving Connaught and the university community to discuss research programs;
- The endowment of a university chair in a field relevant to Connaught;
- And the secondment of staff both to and from Connaught and universities which may lead to the employment of new graduates by Connaught.

9. The lines of communication extending from production through quality control to the president must be clearly defined and rigidly followed. With respect to release of products, the ultimate decision of the director of quality control must be final.

10. Connaught should continue in association with the Red Cross to provide blood products for Canada; collaboration with the Red Cross should be improved. Improvements must be made to the production facilities and procedures in the Blood Products Division at Connaught.

C. *Bureau of Biologics (Canada)*

11. The inadequacies in number of staff, laboratory space and animal facilities at BOB (Canada) must be corrected. (BOB is a bureau of the health protection branch, Department of National Health and Welfare—Ed.) The increase in staff must be sufficient to enable adequate site inspection of all facilities providing biologicals for Canada and to enable adequate laboratory control procedures to be carried out.

12. Research must have a high priority at BOB (Canada) so that it may keep abreast of technological developments in the control of biologicals.

The responsibility for the safety and potency of biologicals used in Canada rests with the Canadian regulatory authority. A free exchange of ideas between Canadian producers and BOB (Canada) should be encouraged rather than allowing dependence on the standards and requirements of another country, the USA, to grow.■